**Manifestation of Subclinical Diabetes Insipidus due to Pituitary Tumor during Pregnancy**

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**Abstract.** We describe a case of diabetes insipidus (DI) due to a pituitary tumor in a 33-year-old pregnant woman who developed a sudden onset of polyuria (over 8 l/day) and polydipsia at 30 weeks of gestation. Her plasma concentration of vasopressin (AVP) was low compared with high serum osmolality (298 mOsm/kg), and her urine output was well controlled by treatment with desmopressin acetate (DDAVP). Cranial magnetic resonance imaging (MRI) demonstrated a 1.8 x 1.2-cm pituitary tumor, but she did not have any disturbance in the release of anterior pituitary hormones. The serum concentration of cystine aminopeptidase (CAP) was within the normal range for a woman at 34 weeks of gestation. After an uncomplicated delivery of a healthy girl, her polyuria gradually resolved. The size of the pituitary tumor gradually decreased in parallel to a reduction in her urine output, but a silent hemorrhage was detected in her pituitary gland 4 weeks after the delivery. Although pregnancy is sometimes associated with central DI, the occurrence of DI due to pituitary tumor under pregnancy is rare. The basal AVP recovered to within the normal range, but the low response of AVP secretion to high osmolality persisted. In this case, pregnancy may affect the manifestation of subclinical DI. This case may therefore enhance our understanding of the mechanisms of DI during pregnancy.

**Key words:** Diabetes insipidus, Pregnancy, Pituitary tumor, Pituitary apoplexy, Cystine aminopeptidase (CAP)

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**PREGNANCY** is sometimes associated with transient polyuria and may unmask subclinical diabetes insipidus (DI) [1, 2]. Various mechanisms of DI during pregnancy have been suggested, for example, insufficient vasopressin (AVP) secretion induced by transient enlargement of the pituitary gland [1, 3], low plasma AVP caused by an elevation in vasopressin dehydrogenase which is thought to be cystine aminopeptidase (CAP) [4], and increased glomerular filtration in pregnancy, but the precise mechanism of this disease remains unknown. We encountered a rare case of DI in a patient with a pituitary tumor whose polyuria developed at 30 weeks of gestation and disappeared following childbirth. The size of the pituitary tumor gradually decreased in parallel with the clinical symptoms of DI. This case may enhance our understanding of the mechanisms of DI during pregnancy.

**Case Presentation**

A 33-year-old primigravida presented with a 3-week history of polyuria and polydipsia in March, 1995. Her symptoms had suddenly developed on
Feb. 10th, 1995 at 30 weeks of gestation, and her urine output exceeded 8–12 l/day on admission. Her past medical history and family history were noncontributory. She denied taking any lithium, calcium or antibiotics. On physical examination, her temperature was 36.6 °C, pulse, 94 beats/min, and blood pressure, 138/81 mmHg. Although her skin was slightly dry, her condition appeared to be good. Her urine output was documented to exceed 8 l/day, and her oral water intake was 5–8 l/day. On admission, her laboratory findings were as follows: the plasma sodium concentration was 139 mEq/l, blood urea nitrogen 2.8 mg/dl, serum creatinine 0.47 mg/dl and uric acid 3.6 mg/dl. The concentration of the total serum protein, liver-function tests, and fasting plasma glucose levels were normal. Although her urinalysis was normal, the specific gravity was 1.000, and urine osmolality was 58 mOsm/kg. Hormonal levels are shown in Table 1. Basal levels of anterior pituitary hormones were within normal ranges. The serum concentration of AVP was low in view of the high serum osmolality (298 mOsm/kg). The daily excretion of urinary AVP was also low (8.2 ng/day). Challenge with desmopressin acetate (DDAVP) demonstrated that her polyuria was responsive to DDAVP (Fig. 1). The CAP activity measured by chromatography was normal for a woman at 34 weeks of gestation. Magnetic resonance imaging (MRI) of her brain demonstrated a pituitary tumor (1.8 x 1.2 cm) with a low intensity signal on a T1-weighted image (WI) and a high intensity signal on a T2-WI (Fig. 2). The tumor appeared to be cystic, such as a Rathke’s cyst, rather than solid.

Table 1. Endocrinological data on manifestations of DI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>ACTH</td>
<td>15.2 pg/ml</td>
</tr>
<tr>
<td>Cortisol</td>
<td>19.1 μg/dl</td>
</tr>
<tr>
<td>Urinary 17OHCs</td>
<td>5.1 mg/day</td>
</tr>
<tr>
<td>Urinary 17KS</td>
<td>2.6 mg/day</td>
</tr>
<tr>
<td>TSH</td>
<td>2.83 μU/ml</td>
</tr>
<tr>
<td>Free triiodothyronine</td>
<td>4.41 pg/ml</td>
</tr>
<tr>
<td>Free thyroxine</td>
<td>0.91 ng/dl</td>
</tr>
<tr>
<td>LH</td>
<td>0.16 mIU/ml</td>
</tr>
<tr>
<td>FSH</td>
<td>0.04 mIU/ml</td>
</tr>
<tr>
<td>GH</td>
<td>2.37 ng/ml</td>
</tr>
<tr>
<td>PRL</td>
<td>186 ng/ml</td>
</tr>
</tbody>
</table>

17OHCS, 17-hydroxycorticoids; 17KS, 17-ketosteroids.

She was treated with DDAVP, 10–15 μg daily via nasal drops, and her urinary output was well controlled. She went into labor during the 37th week of gestation and delivered a healthy girl with a birth weight of 2976 g (Apgar score 9).

Following delivery, since her urinary volume gradually decreased, we could reduce the DDAVP and stop the treatment in the 2nd postpartum week. Cranial MRI in the 4th postpartum week demonstrated no change in tumor size, but the signal on a T1-WI was higher than that taken during the 34th week in gestation and was therefore interpreted as indicating a hemorrhage (Fig. 3B). She denied any change in vision or headache. A wa-
A ter-deprivation test was performed during the 4th postpartum week. Her urine output was 3.5–4 l/day, and her results suggested that she suffered from partial DI (Fig. 4). Anterior pituitary function tests also were performed at this time. The hormonal responses of the anterior pituitary gland to corticotropin-releasing hormone, LHRH, TRH, and GH releasing hormone were normal, except for an impaired response of serum PRL, FSH and LH that is characteristic of the postpartum period (Fig. 5).

She was discharged 6 weeks postpartum, when her urine volume was 1.8-2.5 l/day without additional DDAVP. The time course illustrating the change in urine output is shown in Fig. 6. One month later (during the 8th postpartum week), cranial MRI demonstrated a fluid level with increased intensity in both T1-WI (Fig. 3C) and T2-WI. Hemorrhage within the pituitary tumor was suspected. MRI 1 month later (during the 12th postpartum week) revealed the same high intensity signal, but the region had diminished in size (1.0 × 1.2 cm).

![Fig. 2. Cranial magnetic resonance imaging (MRI) at 34 weeks gestation revealing a pituitary tumor (1.8 × 1.2 cm, arrow) in the sella turcica, with a low intensity signal on T1-weighted images (WI) (A, C) and a high intensity signal on a T2-WI (B). Coronal contrast enhanced T1-WI revealed enhancement only within the wall of the tumor (D).](image-url)

![Fig. 3. Time course illustrating the changes in cranial magnetic resonance imaging (MRI). A: MRI (sagittal T1-WI) performed at 34 weeks gestation. B: At the 4th postpartum week, sagittal T1-WI showing increased signal intensity compared with the previous image, A. C: At the 8th postpartum week, sagittal T1-WI showing increased signal intensity with a fluid level. The size of the tumor appears smaller than that in A (1.0 × 1.2 cm). D: At the 12th postpartum week, MRI did not reveal any changes in the signal intensity of the tumor. E: At the 12th postpartum week, sagittal T2-WI also showing high signal intensity with a fluid level. F: At the 6th postpartum month, the size of the tumor appears much smaller than in A (0.6 × 0.8 cm).](image-url)
The pituitary tumor appeared to be an adenoma, because it changed in size throughout her pregnancy and delivery and caused the subsequent development of apoplexy. Her urinary output was 1-1.5 L/day at that time. Hypertonic-saline-infusion tests were performed in the 2nd and 14th postpartum weeks (the urinary output was 4.5 L/day and 1.3 L/day, respectively), and the results are shown in Fig. 7. Although the basal level of AVP increased by the 14th postpartum week, AVP secretion remained low despite an increase in serum osmolality, which was consistent with subclinical DI. MRI 3 months later (during the 6th postpartum month) revealed that the pituitary tumor had become much smaller (0.6 x 0.8 cm) (Fig. 3F). Currently her urinary excretion and pituitary (Fig. 3D, 3E). The pituitary tumor appeared to be an adenoma, because it changed in size throughout her pregnancy and delivery and caused the subsequent development of apoplexy. Her urinary output was 1-1.5 L/day at that time. Hypertonic-saline-infusion tests were performed in the 2nd and 14th postpartum weeks (the urinary output was 4.5 L/day and 1.3 L/day, respectively), and the results are shown in Fig. 7. Although the basal level of AVP increased by the 14th postpartum week, AVP secretion remained low despite an increase in serum osmolality, which was consistent with subclinical DI. MRI 3 months later (during the 6th postpartum month) revealed that the pituitary tumor had become much smaller (0.6 x 0.8 cm) (Fig. 3F). Currently her urinary excretion and pituitary
Discussion

A woman at 30 weeks of gestation presented with polydipsia and polyuria in the presence of a pituitary tumor with subsequent resolution of her symptoms postpartum. Studies measuring the secretion and action of AVP suggested that she suffered from central DI. Her urinary output decreased gradually in parallel with a reduction in tumor size, and was incidentally associated with hemorrhage. Prior to conception, she denied having either polyuria or polydipsia. Even when her urinary output normalized following delivery, the AVP secretion in response to the hypertonic-saline test was low. She was not operated on for pituitary tumor because her urinary volume normalized and she wanted to have one more baby. The pituitary tumor was therefore not investigated pathologically. The pituitary tumor appeared to be an adenoma, since the size changed throughout her pregnancy and the pituitary hemorrhage occurred in this tumor. Moreover, this tumor was thought to be a non-functioning adenoma, in view of the results of anterior function tests and the lack of hormone levels are all within normal limits, and the pituitary tumor remains under observation.
of amenorrhea, galactorrhea and other endocrinological symptoms during the non-pregnant state.

Polyuria during pregnancy is rare, and its mechanism is still unknown [1]. In the past, several theories have been proposed. In summary they are as follows: (1) The swelling of the anterior pituitary gland during pregnancy compresses the posterior pituitary gland, giving rise to DI [1, 3, 5–8]. (2) The increased glomerular filtration rate in pregnancy increases the requirement for AVP, thus unmasking the partial lack of AVP [9, 10]. (3) Tubular sensitivity to AVP varies in pregnancy [10, 11]. (4) Circulating vasopressin dehydrogenase “vasopressinase”, which may be CAP, is secreted by the placenta and thus gives rise to DI [4, 12, 13]. (5) Increased adrenocorticosteroids, progesterone, and thyroxin in pregnancy antagonizes AVP [1, 9]. (6) To maintain a lower serum osmolality, the set point of AVP secretion decreases and thus the need for AVP increases [14].

During pregnancy, pituitary adenoma cells are enlarged by an increase in estrogen [6]. Moreover, Child et al. [8] and van der Wildt et al. [15] have suggested DI may be the first symptom of a tumor in the hypophyseal-hypothalamic area, especially since some of these tumors are reported to grow during pregnancy. In this case, we believe that the appearance of DI was secondary to the enlargement of the pituitary tumor which compressed the posterior pituitary gland. The reason was that the enlargement of this tumor was much greater than that of the normal anterior pituitary gland. Moreover, her urine volume decreased in parallel with the reduction in the size of her pituitary tumor. However, the low response of AVP secretion to the high osmolality persisted. We therefore believe that she may have had a pituitary tumor and subclinical DI prior to pregnancy that worsened during pregnancy. The two cases mentioned above in which DI was the first symptom of a tumor in the hypophyseal-hypothalamic area were either a craniopharyngioma or a prolactinoma [8, 15]. In one case, DI worsened, and in the other one, surgical excision was required given the onset of visual disturbances. Only in our patient did the polyuria improve following delivery.

It is also interesting that despite hemorrhage within the pituitary tumor postpartum, her symptoms were not exacerbated. In many cases, pituitary hemorrhage causes an acute increase in the size of the tumor leading to DI and/or visual defects [16], but in this case, the symptoms of DI improved despite the occurrence of apoplexy. These findings suggest that the size of the pituitary tumor decreased greatly.

Acute hemorrhage within a pituitary adenoma, classically manifesting as “pituitary apoplexy”, is now a well recognized condition but is relatively uncommon. The incidence of pituitary apoplexy in patients with pituitary tumors is reported to vary from 6 to 16.6% [17–19]. The incidence of pituitary apoplexy during pregnancy is much lower, and only six cases of pituitary apoplexy during pregnancy have been reported (Five patients had a PRL-secreting adenoma and one had acromegaly [7, 20–24]). Many authors have correlated pituitary apoplexy with tumor size [25, 26] and even with increased estrogens, resulting either from medical treatment or from pregnancy [16]. As we mentioned above, pregnancy enlarges the size of the normal pituitary gland and pituitary tumors via the increase in estrogen, so it is not surprising that hemorrhage or hemorrhagic infarction of the tumor may occur. The hemorrhage in this case may have been caused by increased estrogen from pregnancy or by enlargement of the tumor.

In conclusion, this case report is the first example of DI in the presence of a pituitary tumor that correlated with the size of the tumor, in which pituitary apoplexy occurred. Our observation demonstrated that the pituitary tumor enlarged during pregnancy, resulting in the manifestation of subclinical DI. Pregnancy may have a considerable effect on a pituitary tumor.

References


